HAL
open science

Is the effect of mobile phone radiofrequency waves on human skin perfusion non-thermal ?

Nathalie Loos, György Thuróczy, Rania Ghosn, Valérie Brenet-Dufour, Sophie Liabeuf, Brahim Selmaoui, Jean-Pierre Libert, Véronique Bach, Momar Diouf, René de Seze

To cite this version:

Nathalie Loos, György Thuróczy, Rania Ghosn, Valérie Brenet-Dufour, Sophie Liabeuf, et al.. Is the effect of mobile phone radiofrequency waves on human skin perfusion non-thermal ?. Microcirculation, 2013, 20 (7), pp.629-636. 10.1111/micc.12062 . ineris-00961812

HAL Id: ineris-00961812

https://ineris.hal.science/ineris-00961812v1

Submitted on 20 Mar 2014

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Received Date : 04-Jun-2012

Revised Date : 12-Apr-2013

Accepted Date : 12-Apr-2013

Article type : Original Research

Is the effect of mobile phone radiofrequency waves on human skin perfusion non-thermal?

Nathalie Loos [1], György Thuróczy [2], Rania Ghosn [2], Valérie Brenet-Dufour [3], Sophie Liabeuf [3,4], Brahim Selmaoui [2], Jean-Pierre Libert [1], Véronique Bach [1], Momar Diouf [5], René de Seze[2].

[1]PériTox Laboratory (EA 4285-UMI01), Faculty of Medicine, Jules Verne University of Picardy, Amiens, France; [2]PériTox Laboratory (EA 4285-UMI01), National Institute of the Industrial Environment and Risks (INERIS), Verneuil-en-Halatte, France; [3]Clinical Research Centre, Division of Clinical Pharmacology, Amiens University Medical Centre, France; [4]INSERM U1088, Faculty of Pharmacy, Jules Verne University of Picardy, Amiens, France; [5]Direction of Clinical Research and Innovation, Amiens University Medical Centre, France.

Running title: radiofrequency exposure and skin vasomotricity

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/micc.12062

This article is protected by copyright. All rights reserved.

Accepted Article

Corresponding author:

Nathalie Loos, PhD

Laboratoire PériTox, EA 4285-UMI01 Unité mixte INERIS

UFR de Médecine, SFR CAP-Santé (FED 4231)

Université de Picardie Jules Verne

3 rue des Louvels - CS 13602

F-80036 AMIENS cedex 1, FRANCE

Tel.: +33 322 827 898

Fax: +33 322 827 896

E-mail: nathalie.loos@u-picardie.fr

Abstract:

OBJECTIVE: to establish whether skin micro blood flow can be modified by exposure to the radiofrequency waves emitted by a mobile phone when the latter is held against the jaw and ear.

METHODS: Variations in skin micro blood flow and skin temperature in adult volunteers were simultaneously recorded with a thermostatic laser Doppler system during a 20-minute "radiofrequency" exposure session and a 20-minute “sham” session. The skin microvessels' vasodilatory reserve was assessed with a heat challenge at the end of the protocol.

RESULTS: During the radiofrequency exposure session, skin micro blood flow increased (*vs*. baseline) more than during the sham exposure session. The sessions did not differ significant in terms of the skin

This article is protected by copyright. All rights reserved.

Accepted Article

temperature time-course response. The skin microvessels' vasodilatory ability was found to be greater during radiofrequency exposure than during sham exposure.

***CONCLUSIONS*:** Our results reveal the existence of a specific vasodilatory effect of mobile phone radiofrequency emission on skin perfusion.

Keywords: thermostatic laser Doppler flowmetry, skin microcirculation, radiofrequency exposure, skin micro blood flow, skin temperature

LIST OF ABBREVIATIONS

AUC: area under the curve

PU: perfusion unit

SD: standard deviation

SkBF: skin micro blood flow

Tsk: skin temperature

INTRODUCTION

With the increasing use of mobile phones, the question of whether the associated radiofrequency fields have harmful effects on various target organs has become very important. The most frequent complaints relate to (i) a heating feeling when the face is directly in contact with the mobile phone and (ii) headache. Symptoms related to skin vascularization and heating include a burning sensation in the eyes or over the face, skin rashes and sunburn-like redness [1]. It has been shown that the heat released by a mobile phone's electronic components increases the local

This article is protected by copyright. All rights reserved.

Accepted Article

skin temperature (Tsk) [2-3]. However, there is much debate as to whether there is a causal relationship between exposure to mobile phone electromagnetic fields and the occurrence of symptoms unrelated to heating. No correlation between the occurrence of these symptoms and exposure to electromagnetic fields has been demonstrated in double-blind studies [4]. Some researchers have reported changes in cerebral blood flow during and/or after mobile phone exposure [5-9]. Vasodilatory processes in intracranial and extracranial blood vessels may be related to the self-reported symptoms (such as headache and tinnitus) that occur during exposure to electromagnetic fields [10-15]. Only one study has shown that facial skin micro blood flow (SkBF) could be modified by mobile phone exposure when the phone was in contact with the skin [16]. However, the latter study did not feature a control situation (e.g. a sham exposure session) and did not monitor Tsk (which is known to influence SkBF). Hence, it is difficult to say whether the observed increases in SkBF were solely due to the heat produced by the mobile phone. Lastly, the ambient temperature (which can also influence the skin's blood flow reactivity) was not controlled [16].

Objectives:

We sought to establish whether the elevation of SkBF induced by mobile phone contact could be solely explained by the heating produced by the device when either emitting radiofrequency waves (in an exposure session) or not (in a sham session). To this end, control exposures were performed (i.e. a sham session versus radiofrequency exposure) and the room's ambient temperature was closely controlled. The same sets of parameters were measured on the other side of the face (i.e. to compare the exposed side with the non-exposed side), in order to determine whether a putative effect affected the exposed side only or (through a systemic reaction) both sides of the face. To check these hypotheses, SkBF and Tsk were recorded at the same sites during sham exposure (i.e. heating only) and radiofrequency exposure (i.e. heating + radiofrequency exposure) on the exposed and non-exposed sides of the face.

This article is protected by copyright. All rights reserved.

Accepted Article

Moreover, the potential effect of mobile phone use on skin microvessel reactivity has never previously been studied. Here, we studied this parameter by applying a heat challenge under the various exposure conditions.

MATERIALS AND METHODS

Inclusion/exclusion criteria and characteristics of the study population

Twenty Caucasian, healthy, young adult volunteers were included in this two-session study. The protocol was approved by the local independent ethics committee (*Comité de Protection des Personnes Nord-Ouest II*, Amiens, France). The trials were performed in a licensed facility (Clinical Research Centre, South Hospital, Amiens University Hospital, Amiens, France). The characteristics of the study population were as follows: 12 women, 8 men; mean ± standard deviation (SD) age: 25 ± 3.9 yr; body weight: 68.3 ± 11.4 kg; height: 173 ± 9.5 cm, systolic/diastolic blood pressure: 121/75 ± 12/9 mmHg; resting heart rate: 69 ± 9 bpm, pulse oxygen saturation: 98.2 ± 0.6 % (using an SpO_2/blood pressure/heart rate monitor from CIC MED, Amiens, France). The subjects were told not to take vasoactive or anti-inflammatory drugs for the 10 days preceding the study. Subjects known to have a personal medical history of hypertension, diabetes, hypercholesterolemia or any cardiovascular, sensory or neurological disease were excluded from the study. Tea, coffee and alcohol were forbidden on the day before the experiments. The subjects did not exercise or consume food for at least 1h prior to each experiment. The use of facial cosmetics was prohibited, although male subjects had to have shaved on the day of the experiment. The test sessions were performed at the same time of the day, in order to minimize ultradian variations in cutaneous vascular parameters. Subjects wore light clothes and were studied in a semi-recumbent, supine position. The subject was not covered with a blanket. The room temperature was kept constant at 24.0 ± 0.6 °C (relative humidity: 45-50%; air velocity: ≤0.10 $m.s^{-1}$, i.e. natural convection conditions). The bed was located in the centre of a naturally lit room (i.e. far from the windows, in order to reduce air currents and

This article is protected by copyright. All rights reserved.

Accepted Article

radiative heat exchanges). Potentially conductive jewellery (ear-rings, etc.) was prohibited, to avoid disturbance of the laser Doppler signals.

Laser Doppler measurements of SkBF and Tsk

Laser Doppler system. A thermostatic laser Doppler system (Flowmeter Periflux System 5010, Perimed, France) was used to continuously record SkBF and Tsk. This method has a high time resolution and has been specifically designed for studying SkBF at a wavelength of 780 nm. The system measures local skin microcirculatory blood perfusion provided by the arterioles and arteriovenous anastomoses. Relative SkBF was expressed in perfusion units (PUs), which corresponds to the number of blood cells in the measured volume multiplied by the latter's mean velocity.

Calibration. The equipment was calibrated before each session. The arbitrary PU was directly related to a physical motility standard, which is based on the signal produced by Brownian motion in a 0.5% suspension of 0.48 µm diameter polystyrene microspheres at 20°C (normal value: 250 ± 5 PU).

Measurements. To investigate changes over time in SkBF and Tsk at the same anatomical site, two small, angled, thermostatic laser Doppler probes (PROBE 457, Perimed, France) were stuck to the cheek (1 cm in front of the ear lobe) on the ipsilateral side (i.e. the side exposed to mobile phone) and the contralateral (non-exposed) sides of the face. Particular care was taken to firmly attach the probes to the skin with special laser-translucent, double-sided adhesive strips (PF 105-3, Perimed) that avoided local vasoconstriction. Each probe contained two optical fibres; one carried the laser beam to the tissue, whereas the other captured the beam back-scattered from the tissue and carried it to the photodetectors for conversion into an electronic signal. Flow measurements were coupled with temperature recordings in the

This article is protected by copyright. All rights reserved.

Accepted Article

same skin area; the thermostatic probe was integrated into the miniature, spherical laser Doppler probe (with a black, insulating, protective envelope; diameter: 10 mm; thickness: 8 mm; fibre separation: 0.25 mm). These thermostatic laser Doppler probes were also used to measure blood perfusion during a local heat challenge performed at the end of the protocol and in which the thermostatic system warmed the whole tissue area under the probe (i.e. 1 cm in diameter).

Radiofrequency exposure and dosimetry

The exposure and sham session were performed in random order. The "radiofrequency" or "sham" mobile phone was positioned against the left ear (using a helmet-like holder), as during normal vocal mode use. The holder freed the subject from the need to hold the mobile phone over the laser Doppler probe without changing the position or pressure. Hence, the mobile phone touched (but did not greatly press against) the thermostatic laser Doppler probe. The subjects were exposed to a commercially available, dual-band GSM mobile phone (PHOENIX, model: Nokia 6650). The phone was connected to a personal computer to standardize and set the required frequency and radiofrequency power using service software (Nokia Corp., Finland). The participants received GSM-modulated exposure at the mobile phone's full power (peak: 2 W; average: 250 mW, pulse modulated with a 1/8 duty cycle) at 900 MHz for 20 minutes. During the exposure, the phone was placed so that its long axis was aligned with an imaginary line from the opening of the ear canal to the corner of the mouth. Actual or sham radiofrequency exposure was performed by respectively connecting a 50-Ohm resistive load or an open-circuit dummy load to the mobile phone's remote antenna connector. The resistive load and the open-circuit dummy load had the same shape and structure, in order to maintain the study's double-blind nature.

The specific absorption rate (W/kg) was measured with a twin Specific Anthropomorphic Mannequin phantom (Antennessa, Rennes, France) filled with standard brain tissue-equivalent liquid (Satimo, Brest,

This article is protected by copyright. All rights reserved.

Accepted Article

France). A small electric field probe (O6-EP64, Satimo, Brest, France) connected to a microvoltmeter (Keithley Instruments Inc., Cleveland, OH, USA) was used to measure the electric field strength within the liquid. Calibration was based on immersing an open-ended coaxial cable connected to a vector network analyser (Wiltron 360B, Anritsu-Wiltron Company, Morgan Hill, CA, USA). The phone was held against the phantom in the ‘‘touch position’’ with a non-metallic holder, according to the European Committee for Electrotechnical Standardization (CENELEC) standard EN 50361 [17]. The probe was moved by a servo-driven XYZ positioning system fitted with a robotic 3D stepper motor (Charlyrobot SA, France). The maximum specific absorption rate was 0.49 W/kg, when averaged over 10 g of tissue. To confirm the effectiveness of the load, the sham mobile phone's specific absorption rate and surface electric field were measured. Indeed, the specific absorption rate for the sham mobile phone was below the system's limit of detection (0.001 W/kg) at all positions on the phantom. No radiofrequency fields were detected at the sham mobile phone's surface.

Protocols

A rest period of at least 30 minutes was imposed (so that the Tsk could stabilize) before SkBF measurements. The subject was instructed not to speak or smile, so as not to disturb the laser Doppler signal. All sources of noise and distraction (music, nearby conversations, etc.) were excluded. The subject was instructed to relax, avoid intense mental activity and remain in a state of quiet wakefulness with his/her eyes open. Two crossover exposure sessions were performed under double-blind conditions, with “radiofrequency” and "sham” exposure in random order and by using the corresponding phones. Each exposure was preceded by a 5-minute control baseline period. The phone was carefully removed (without touching the laser Doppler probe) after 20 minutes of exposure, in order to mimic actual mobile phone use. Mean values of SkBF were analyzed for 1-minute blocks of continuous recordings at the following time points in each session: (i) 5 minutes before the start of exposure (as a baseline control, before placing

This article is protected by copyright. All rights reserved.

Accepted Article

the phone against the ear), (ii) after 1, 5, 10, 15 and 20 minutes of actual or sham exposure and (iii) 1, 5, 10, 15 and 20 minutes after the end of actual or sham exposure. A heat challenge was performed 25 minutes after the end of exposure by locally heating both sides of the face to 44°C for 1 minute, followed by a 30-minute period for the return to baseline. This hyperthermia challenge induces local hyperaemia, which reflects the skin microvessels' ability to dilate in response to heating [18]. This early increase in perfusion was stable for some minutes (a typical example is shown in Figure 1). This early perfusion peak is related to local nervous sensory activity only and not to systemic endothelial activity (e.g. nitric oxide mechanisms), which appear later (at the called "plateau") during prolonged, heat-induced vasodilatation [19-22].

Data processing and statistics

Data processing. Data were sampled at 32 Hz, stored and then analyzed using Perisoft software (version 2.10, Perimed). Output data were exported and processed with Microsoft Excel® (version 2007) and then GraphPad Prism® software (version 5.02, GraphPad Software, San Diego, CA, USA). Analyses of variance (ANOVAs) and post-hoc analyses were performed with SAS® software (version 9.2, SAS Institute Inc., Cary, NC). Descriptive parameters for our population were presented as mean ± SD for quantitative variables. For the analysis of baseline values, a mixed ANOVA model with random intercept was used to study a possible relationship between exposure conditions (radiofrequency *vs*. sham exposure), the side of the face (the mobile phone side *vs*. the control side) and SkBF (an independent variable). The threshold for statistical significance was set to 0.05. A Wilcoxon signed rank test was used to perform pairwise comparisons of SkBF on the mobile phone side and on the control side of the face during the radiofrequency session. As two comparisons were performed, Bonferroni-Holm adjusted p-values were computed to control for inflation of the type 1 error.

This article is protected by copyright. All rights reserved.

Accepted Article

The main SkBF parameters were then calculated: the area under the curve (AUC) and the maximum value (Max) recorded in the first 20 minutes of exposure provide accurate indexes of the time course of the blood flow. As there was no change in SkBF or skin temperature on the contralateral side of the face during either the radiofrequency or the sham exposure, these data for that side were not analyzed further. The normality of the data distribution for SkBF and Tsk AUC and Max on the phone side was then checked with the D'Agostino-Pearson omnibus K2 test. The radiofrequency and sham sessions were then compared for the exposed side of the face using a Student's paired t-test. A Bonferroni-Holm correction was applied when multiple tests were performed on non-independent variables: for the two tests applied to the AUC and Max, the p-value was multiplied by a factor of 2. The same tests were used to compare Tsk data in the two exposure conditions.

Due to the well-known overall asymmetry of blood flow when comparing the left and right sides of the face [23-24], heat challenge responses for the phone-exposed side and the contralateral side cannot be compared directly. Hence, the radiofrequency and sham exposure sessions were compared for each side of the face separately.

RESULTS

Baseline period:

Skin perfusion.

For a given side of the face, the radiofrequency and sham exposure sessions did not differ significantly in terms of the SkBF (radiofrequency SkBF = 25.5±14.2 PU; sham SkBF = 28.4±13.1 PU; p=0.15, paired-*t*-test in 20 subjects for the exposed side of the face; radiofrequency SkBF = 28.6±12.4 PU; sham SkBF = 32.6±13.6 PU; p=0.13, for the contralateral side).

This article is protected by copyright. All rights reserved.

Accepted Article

For the radiofrequency exposure session, the mean baseline SkBF on the exposed side of the face did not differ significantly from the value on the contralateral side: p=0.25. For the sham exposure session, the mean baseline SkBF was slightly lower on the exposed side than on the contralateral side: p=0.04.

Skin temperature. For the radiofrequency exposure session, the mean baseline Tsk on the exposed side of the face was 33.0±0.6°C and differed significantly from that on the contralateral side of the face (33.3±0.7°C, p=0.02). This inter-side difference was not found for the sham exposure session (33.2±0.7°C *vs.* 33.3±0.8°C, p=0.39). The radiofrequency and sham exposure sessions did not differ significantly in terms of the mean baseline Tsk on the exposed side of the face (p=0.22) or on the contralateral (non-exposed) side (p=0.97).

Exposure period:

On the control side of the face, the sham and radiofrequency exposure sessions gave rise to similar response profiles for the mean SkBF and mean Tsk values (Figures 2A and 2B). During radiofrequency exposure, the SkBF on the exposed side was much greater during radiofrequency exposure than during sham exposure (p=0.0496 for SkBF AUC (t=3.1; df=19) and p=0.0062 for SkBF Max (t=2.1; df=19), in pairwise comparisons). No significant radiofrequency *vs.* sham difference was observed for the skin temperature Tsk (p>0.05).

The heat challenge:

When heating the skin locally to 44°C on both sides of the face at the same time, the early peak value for SkBF (i.e. the raw data after 1 minute) on the exposed side of face was significantly greater after the radiofrequency exposure session than after the sham exposure session (p<0.0001) (Figure 3). As a

This article is protected by copyright. All rights reserved.

Accepted Article

positive control, no difference on the contralateral (non-exposed) side was found when comparing radiofrequency and sham exposure sessions (201 ± 66 PU *vs.* 186 ± 65 PU, respectively; p=0.28).

DISCUSSION

Anatomical and physiological links between peripheral and central (intracranial) vascularization allow heat exchanges between blood vessels in the face and those of the brain. It is known that selective brain cooling can occur during hyperthermia (such as during intensive physical exercise, in a warm bath or in fever situations) [25-26]. In an attempt to maintain a constant brain temperature, the rise in body temperature (up to 39°C) triggers an increase in blood flow from the brain to the face (notably through the emissary veins) [25-29]. In the present study, the absence of a blood flow increase on the contralateral side of the face means that the observed effect was local and was not related to hemodynamic changes in the body as a whole (which would have been evidenced on both sides of the face). Hence, it is unlikely that cutaneous heating induced by a mobile phone can trigger significant hemodynamic changes in cerebral vessels via the conductive heating of blood *per se*. An echo Doppler study performed under the same experimental conditions and with the same radiofrequency exposure did not show any significant change in flow from the brain arteries [30]. These observations show that the brain's haemodynamics were not perturbed by local skin heating.

During the baseline control period, the raw PU values were relatively low and constant for each subject. This indirectly reflects the skin vasomotor tone activity (mainly controlled by the vasoconstrictor α_1-adrenergic nervous system) at a comfortable, thermoneutral ambient temperature of 24°C for humans wearing light clothing at rest [31-34]. Direct heating effects at ~+2°C over baseline (i.e. increases in Tsk due to the mobile phone's electronic components) were observed in both sham and radiofrequency

This article is protected by copyright. All rights reserved.

Accepted Article

exposure sessions. This corresponds to the well-known "passive vasodilation" phenomenon (inducing an increase in SkBF) caused by a decrease in the baseline sympathetic vasoconstrictor tone [35-36].

By assessing Tsk with an infrared camera, Straume et *al*. also observed similar heating after 30 minutes of exposure to a mobile phone [3]. Using a laser Doppler technique, Monfrecola et *al*. [16] concluded that SkBF was greater with a mobile phone turned on than with a mobile phone turned off. However, as there was no sham group, it is difficult to say whether this finding was related to the study design or to a specific effect of radiofrequency exposure. Skin temperature was not recorded at the same time as SkBF. Moreover, the room temperature was not reported and it is known that ambient temperature can strongly modify peripheral skin vasomotricity. Hence, it was impossible to say whether or not the elevation of SkBF was solely due to the local heating produced on skin by the mobile phone. In the present study, we simultaneously measured SkBF and Tsk with the same spatiotemporal resolution. We found that skin vasodilation on the mobile phone side of the face was much greater during radiofrequency exposure than during sham exposure - even though the two sessions did not differ significantly in terms of Tsk (i.e. an increase of 2.7°C over the baseline after 20 min of radiofrequency exposure or sham exposure). Given that the Tsk curves for sham and radiofrequency exposure sessions were exactly the same (i.e. superimposable, with a mean temperature at 20 min=35.9°C in both sessions), the difference in SkBF curves between the radiofrequency exposure session (mean SkBF at 20 min=65 PU) and the sham session (mean SkBF at 20 min=40 PU) exposures can be attributed to a specific effect of radiofrequency waves on the skin's microcirculation. The SkBF curve of the radiofrequency exposure session reflects the sum of the radiofrequency effect and the heating effect due to the mobile phone's battery and electronic components.

This article is protected by copyright. All rights reserved.

Accepted Article

Our results show for the first time that the effect of radiofrequency exposure on skin vasomotricity reported by Monfrecola et *al.* [16] (see the SkBF data for the radiofrequency-exposed side in the present study) potentiates the electronic components' thermal influence (see the SkBF data for on sham exposed side) and is non-thermal.

It is important to emphasize that the measurements of local cutaneous temperature were performed under normal conditions, i.e. the cutaneous temperature under the laser Doppler probe was not controlled thermostatically. This is possible because the ambient temperature was closely controlled and the subject was close to thermoneutrality (see *Materials and Methods* section). In this case, the overlap between the two curves of exposure session (see Figure 2B) is real.

As mentioned above, the SkBF corresponds to the product of the blood cell velocity and the concentration of moving blood cells. Since cannot vary of the studied here, a larger signal must be due to an increase in blood cell velocity, which at the capillary level can only result from an increase in arteriolar diameter, i.e. vasodilation. The latter can be caused by two main processes: inhibition of the sympathetic, noradrenergic vasoconstrictor system and activation of the non-noradrenergic, active vasodilatory system. Cutaneous vasodilation can be due to the release of sympathetic noradrenergic vasoconstrictor tone [35-36]. The main contributors to non-adrenergic vasodilation are endothelial factors such as nitric oxide, vasoactive intestinal peptide, neuropeptide Y, substance P and histamine [36-39]. These neuronal and endothelial factors can modify the basal arteriolar myogenic tone [40], which has been defined as “a maintained basal state of contraction which arises within a muscle, without involvement of external factors” [41]. Possible ways of determining the process that is predominantly involved in the effect observed here will be discussed below.

This article is protected by copyright. All rights reserved.

Accepted Article

The hyperaemic response

During application of a 1-minute post-exposure heat challenge, the hyperaemic response showed that radiofrequency exposed skin microvessels dilated more than sham-exposed microvessels did.

Given that the laser Doppler technique uses 2 measurement probes (one for each side of the face), the two sides' respective hyperaemic responses to the heat challenge cannot be compared because it is known that SkBF values differ from one anatomical site to another in a given person [23-24]. Hence, the heat challenge on the contralateral (non-exposed) side was just used to check that the challenge was working well (i.e. as a positive control). The radiofrequency and sham exposure sessions were always compared for the same side of the face.

The radiofrequency-exposed vessels thus appeared to have a larger vasodilatory reserve at the onset of the hyperaemic response. Dilatory ability depends on the mechanical properties of the skin arterioles and arteriovenous anastomoses, which act as resistances. Hence, large changes in the vessels' diameter can trigger substantial changes in SkBF [42]. The vasoconstrictor tone of the skin's microvessels (mainly the arterioles) is abolished during this "early" peak of the hyperaemic response (within the first minute of heating) [43]. It is important to bear in mind that a neuropeptide-Y-mediated nociceptive loop reflex is activated when the skin is heated above 42°C (as was the case here for the heat challenge) [44-45]. Our results suggest that this reflex could be exacerbated by radiofrequency exposure (relative to sham exposure), since the skin vessels' hyperaemic response was much stronger. The facial skin's nervous inputs are also connected to the trigeminal sensory nuclear complex, which receives somatosensory inputs and provides feedback modulation to higher brain centres [46-48]. It would be interesting to see whether or not these loop-reflex nervous mechanisms are involved by chemically inhibiting their activity.

This article is protected by copyright. All rights reserved.

Accepted Article

Conclusion

By measuring SkBF and controlling Tsk with the same spatiotemporal resolution in human subjects at thermoneutrality, we identified specific, athermal modifications of the skin blood flow during mobile phone radiofrequency exposure. The cumulative effect of radiofrequency exposure and heating by the mobile phone leads to strong increases in skin perfusion. The athermal effects of radiofrequency exposure on SkBF were seen both during and after acute exposure.

Perspectives

Further research is now required to understand the physiological mechanisms that underlie the observed changes in the activity of the neurogenic and non-neurogenic components controlling skin vasomotricity. One such approach could involve a fast Fourier transform analysis of the laser Doppler perfusion signal over several minutes: low observed frequencies would suggest a myogenic mechanism (0.02-0.06 Hz) and high frequencies would suggest a neurogenic mechanism (0.06-0.2 Hz). Given that the vasodilatory mechanisms controlling skin vasomotion are more active during radiofrequency exposure than during sham exposure, it would be interesting to see whether or not the increase in SkBF (on the mobile phone side) is due to a change in the sympathetic activity controlling vasomotor tone [35-36]. The relative contribution of various vasodilators (mediated by neurogenic and non-neurogenic processes) could be investigated by using intradermal microdialysis [38] and the administration of specific inhibitors (such as L-nitroarginine methyl ester for nitric oxide) [37]. It would also be interesting to look at the possible long-term consequences of repeated increases in vasodilatation.

This article is protected by copyright. All rights reserved.

Accepted Article

Accepted Article

ACKNOWLEDGMENTS

We thank the staff at the Clinical Research Centre at Amiens University Hospital for their help in recruiting and selecting subjects and for performing the clinical examinations. We also thank Joe Wiart for providing the experimental facility for radiofrequency dosimetry and Sami Savela and Jafar Keshvari for technical assistance with the mobile phone test software used in the study. We thank Jonathan Meynier (Clinical Research Centre, North Hospital, Amiens, Picardy, France) for his expertise in statistical analysis and David Fraser (Biotech Communication SARL, Damery, France) for advice on the manuscript's English.

REFERENCES

1. Röösli M. Radiofrequency electromagnetic field exposure and non-specific symptoms of ill health: a systematic review. Environ Res. 107:277-287, 2008.

2. Anderson V, Rowley J. Measurements of skin surface temperature during mobile phone use. Bioelectromagnetics. 28:159-162, 2007.

3. Straume A, Oftedal G, Johnsson A. Skin temperature increase caused by mobile phone: a methodological infrared camera study. Bioelectromagnetics. 26:510-519, 2005.

4. World Health Organisation. Electromagnetic fields and public health: Electromagnetic Hypersensitivity. WHO factsheet 296, 2005.

5. Huber R, Treyer V, Borbély AA, Schuderer J, Gottselig JM, Landolt HP, Werth E, Berthold T, Kuster N, Buck A, Achermann P. Electromagnetic fields, such as those from mobile phones, alter regional cerebral blood flow and sleep and waking EEG. J Sleep Res. 11(4):289-295, 2002.

This article is protected by copyright. All rights reserved.

Accepted Article

6. Huber R, Treyer V, Schuderer J, Berthold T, Buck A, Kuster N, Landolt HP, Achermann P. Exposure to pulse modulated radio frequency electromagnetic fields affects regional cerebral blood flow. Eur J Neurosci. 21:1000-1006, 2005.

7. Haarala C, Aalto S, Hautzel H, Julkunen L, Rinne JO, Laine M, Krause B, Hamalainen H. Effects of a 902 MHz mobile phone on cerebral blood flow in humans: A PET study. Neuroreport. 14:2019-2023, 2003.

8. Aalto S, Haarala C, Brück A, Sipilä H, Hämäläinen H, Rinne JO. Mobile phone affects cerebral blood flow in humans. J Cereb Blood Flow Metab. 26(7):885-890, 2006.

9. Volkow ND, Tomasi D, Wang GJ, Vaska P, Fowler JS, Telang F, Alexoff D, Logan J, Wong C. Effects of cell phone radiofrequency signal exposure on brain glucose metabolism. JAMA. 305(8):808-813, 2011.

10. Moskowitz MA, Reinhard JF Jr, Romero J, Melamed E, Pettibone DJ. Neurotransmitters and the fifth cranial nerve: is there a relation to the headache phase of migraine? Lancet. 2(8148):883-885, 1979.

11. Vass Z, Shore SE, Nuttall AL, Miller JM. Direct evidence of trigeminal innervation of the cochlear blood vessels. Neuroscience. 84(2):559-567, 1998.

12. Abdel-Rassoul G, Abou El-Fateh O, Abou Salem M, Michael A, Farahat F, El-Batanouny M, Salem E. Neurobehavioral effects among inhabitants around mobile phone base stations. NeuroToxicology. 28: 434-440, 2007.

13. Hutter HP, Moshammer H, Wallner P, Kundi M. Subjective symptoms, sleeping problems, and cognitive performance in subjects living near mobile phone base stations. Occup Environ Med 63:307-313, 2006.

This article is protected by copyright. All rights reserved.

Accepted Article

14. Hutter HP, Moshammer H, Wallner P, Cartellieri M, Denk-Linnert DM, Katzinger M, Ehrenberger K, Kundi M. Tinnitus and mobile phone use. Occup Environ Med.67: 804-808, 2010.

15. Chia SE, Chia HP, Tan JS. Prevalence of Headache among Handheld Cellular Telephone Users in Singapore: A Community Study. Environ Health Perspect. 108:1059-1062, 2000.

16. Monfrecola G, Moffa G, Procaccini EM. Non-ionizing electromagnetic radiations, emitted by a cellular phone, modify cutaneous blood flow. Dermatology. 207:10-14, 2003.

17. CENELEC EN 50361, Basic Standard for the measurement of Specific Absorption Rate related to human exposure to electromagnetic fields from mobile phones (300 MHz-3 GHz). CENELEC, 2002.

18. Minson CT. Thermal provocation to evaluate microvascular reactivity in human skin. J Appl Physiol. 109(4):1239-46, 2010.

19. Charkoudian N. Skin blood flow in adult human thermoregulation: how it works, when it does not, and why. Mayo Clin Proc. 78:603-612, 2003.

20. Roustit M, Cracowski JL. Non-invasive assessment of skin microvascular function in humans: an insight into methods. Microcirculation. 19(1):47-64, 2012.

21. Boccalon H. Doppler au laser: méthodes d'exploration de la microcirculation chez l'homme. In: Masson, edited by Microcirculation clinique. Paris.1996, p. 91-108.

22. Cracowski JL, Minson CT, Salvat-Melis M, Halliwill JR. Methodological issues in the assessment of skin microvascular endothelial function in humans. Trends Pharmacol. Sci. 27(9):503-508, 2006.

23. Johnson JM, Taylor WF, Shepherd AP, Park MK. Laser-doppler measurement of skin blood flow: comparison with plethysmography. J Appl Physiol. 56(3):798-803, 1984.

This article is protected by copyright. All rights reserved.

24. Benedicic M, Dolenc VV, Stefanovska A, Bosnjak R. Left-right asymmetry of the facial microvascular control. Clin Auton Res. 16(1):58-60, 2006.

25. Boulant JA. Neuronal basis of Hammel's model for set-point thermoregulation. J Appl Physiol. 100(4):1347-1354, 2006.

26. Cabanac M, Caputa M. Open loop increase in trunk temperature produced by face cooling in working humans. J Physiol. 289:163-174, 1979.

27. Hertzman AB, Randall WC, Piess CN, Seckendorf R. Regional rates of evaporation from skin at various environmental temperatures. J Appl Physiol. 5:153-161, 1953.

28. Caputa M, Kadziela W, Narebski J. Significance of cranial circulation for the brain homeothermia in rabbits. II. The role of the cranial venous lakes in the defence against hyperthermia. Acta Neurobiol Exp. 36(6):625-37, 1976.

29. Narebski J. Human brain homeothermy during sleep and wakefulness: an experimental and comparative approach. Acta Neurobiol Exp. 45(1-2):63-75, 1985.

30. Ghosn R, Thuróczy G, Loos N, Brenet-Dufour V, Liabeuf S, de Seze R, Selmaoui B. Effects of GSM 900 MHz on Middle Cerebral Artery Blood Flow Assessed by Transcranial Doppler Sonography. Radiat Res. 178(6):543-550, 2012.

31. Hardy JD, Du Bois EF. Differences between men and women in their responses to heat and cold. Proc. Natl. Acad. Sci. 26:389-398, 1940.

32. ISO 2005. Ergonomics of the Thermal Environment Analytical Determination and Interpretation of Thermal Comfort Using Calculation of the PMV and PPD Indices and Local Thermal Comfort Criteria Geneva, International Organization for Standardization. 2005

This article is protected by copyright. All rights reserved.

Accepted Article

33. Natsume K, Ogawa T, Sugenoya J, Ohnishi N, Imai K. Preferred ambient temperature for old and young men in summer and winter. Int. J. Biometeorol. 36:1-4, 1992.

34. Tanaka M, Desruelle AV, Sari H, Candas V, Tanaka K, Maeda T. Effects of Decreasing Air Temperature on Peripheral Thermal Reactions in Males and Females Masatoshi. Environ Health Prev Med. 8:178-183, 2003.

35. Rasch W, Cabanac M.Vasomotor response of the human face: laser-Doppler measurements during mild hypo- and hyperthermia. Acta Physiol Scand. 147(4):431-6, 1993.

36. Charkoudian N. Mechanisms and modifiers of reflex induced cutaneous vasodilation and vasoconstriction in humans. J Appl Physiol 109: 1221-1228, 2010.

37. Kellogg DL Jr, Zhao JL, Wu Y. Neuronal nitric oxide synthase control mechanisms in the cutaneous vasculature of humans in vivo. J Physiol 586: 847-857, 2008.

38. McCord GR, Cracowski JL, Minson CT. Prostanoids contribute to cutaneous active vasodilation in humans. Am J Physiol Regul Integr Comp Physiol 291: R596-R602, 2006.

39. Zhao M, Bai H, Wang E, Forrester JV, McCaig CD. Electrical stimulation directly induces pre-angiogenic responses in vascular endothelial cells by signaling through VEGF receptors. J Cell Sci. 117(3):397-405, 2004.

40. Osol G, Brayden J. Prologue: vascular myogenic mechanisms. Am J Physiol Heart Circ Physiol. 283: H2157-H2159, 2002.

41. Johansson B. Myogenic tone and reactivity: definitions based on muscle physiology. J Hypertens Suppl. 7: S5-S8, 1989.

42. Lossius K, Eriksen M, Walløe L. Fluctuations in blood flow to acral skin in humans: connection with heart rate and blood pressure variability. J Physiol. 460:64-655, 1993.

This article is protected by copyright. All rights reserved.

Accepted Article

43. Robertson D, Biaggioni I, Burnstock G, Low PA, Paton JFR. In: Primer on the autonomic nervous system. Edited by Elsevier, Third Edition, 2012.

44. Hodges GJ, Jackson DN, Mattar L, Johnson JM, Shoemaker JK. Neuropeptide Y and neurovascular control in skeletal muscle and skin. Am J Physiol Regul Integr Comp Physiol. 297:R546-R555, 2009.

45. Stephens DP, Saad AR, Bennett LA, Kosiba WA, Johnson JM. Neuropeptide Y antagonism reduces reflex cutaneous vasoconstriction in humans. Am J Physiol Heart Circ Physiol. 287: H1404-H1409, 2004.

46. Kuypers HG. Central cortical projections to motor and somato-sensory cell groups. An experimental study in the rhesus monkey. Brain. 83:161-184, 1960.

47. Dunn RC Jr, Tolbert DL. The corticotrigeminal projection in the cat. A study of the organization of cortical projections to the spinal trigeminal nucleus. Brain Res. 240(1):13-25, 1982.

48. Vass Z, Shore SE, Nuttall AL, Miller JM. Direct evidence of trigeminal innervation of the cochlear blood vessels. Neuroscience. 84(2):559-67, 1998.

Legends for illustrations

Figure 1. A typical example of a skin hyperaemic response after a 1-minute heat challenge.

Figure 2. Raw data of mean skin perfusion (A) and the corresponding local skin temperature (B) during 20 minutes of exposure to mobile phone radiofrequency radiation and then for 20 minutes after the end of exposure.

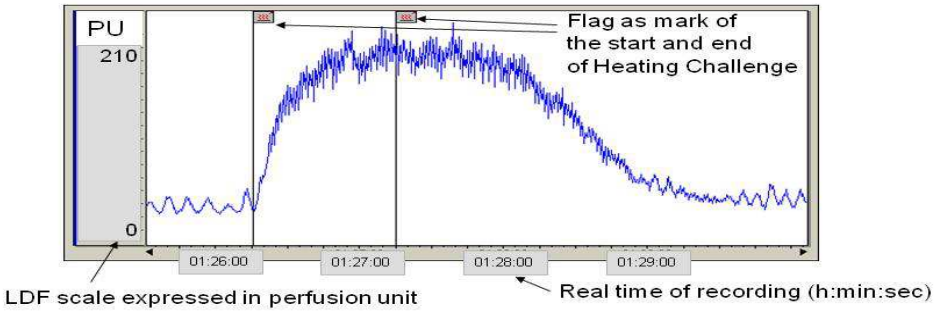
This article is protected by copyright. All rights reserved.

Accepted Article

Legend: Data for one-minute periods are expressed as the mean ± SD in 20 young adult subjects at baseline (0) and after 1, 5, 10, 15 and 20 minutes of real or sham exposure and then 1, 5, 10, 15 and 20 minutes after the end of radiofrequency or sham exposure. Raw skin perfusion data are expressed in arbitrary perfusion units (PUs). The skin temperature is expressed in °C. The conditions are as follows: SkBF on the side of the head with the real mobile phone (RF-S_{MP}: black circles) and on the contralateral side (RF-S_{CTR}: white circles), during and after a radiofrequency exposure session; SkBF on the side of the head with the sham mobile phone (Sham-S_{MP}: black squares) and on the contralateral side (Sham-S_{CTR}: white squares), during and after a sham exposure session.

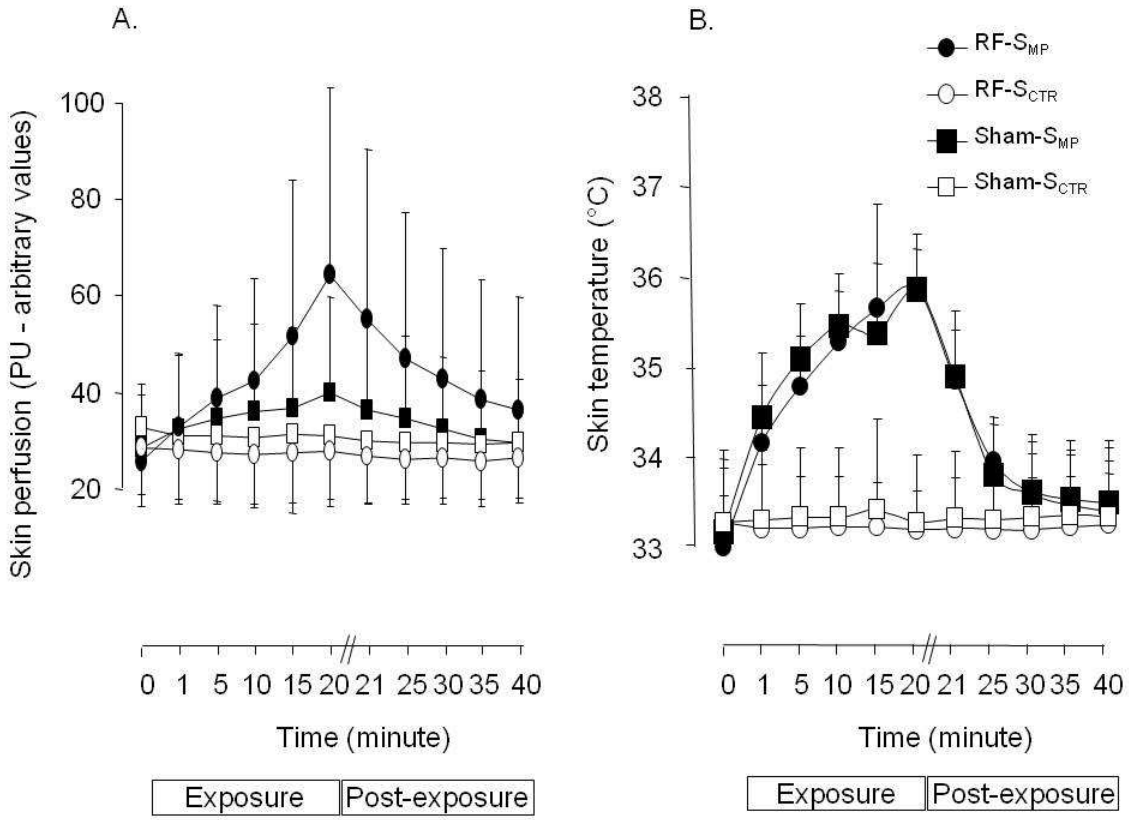
Figure 3. Maximum skin perfusion during the heat challenge.

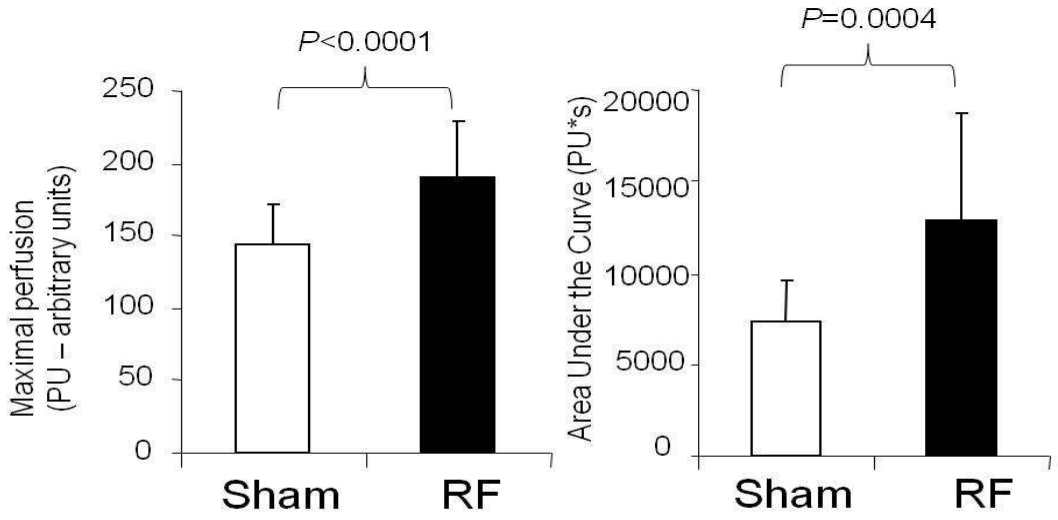
Legend: raw skin perfusion data (expressed in perfusion units, PU) and area under the curve are presented as mean ± SD values in 20 subjects during maximal vasodilatation at 44°C for a 1 min period following radiofrequency exposure at the side of the head with the mobile phone (i.e. the exposed side). Statistically significant differences between radiofrequency (RF) and sham exposures are indicated by *P*.



This article is protected by copyright. All rights reserved.

Accepted Article





This article is protected by copyright. All rights reserved.